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Alkhabaz, A; Pujari, R; Ren, Y; Smith, SJ; Liao, YJ.

Corresponding author:

Anas Alkhabaz

alkhabaz@stanford.edu

Author Affiliation:

Stanford University.

ADMINISTRATIVE INFORMATION**Support** - None.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202510029**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 January 2025 and was last updated on 9 January 2025.**INTRODUCTION**

Review question / Objective This systematic review aims to explore the impact of different treatment modalities on visual outcomes in patients with optic disc drusen-associated neovascularization.

Rationale Choroidal neovascularization (CNV) is a vision-threatening complication that results from various underlying causes, most commonly age-related macular degeneration. Optic disc drusen (ODD) is a rare cause of CNV that is relatively prevalent in the pediatric population. Management of ODD-CNV poses a challenge due to its proximity to the papillo-macular bundle, damage to which can result in subsequent vision loss. Multiple modalities have been explored including laser photocoagulation, photodynamic therapy, surgery, and most recently anti-VEGF agents. However, due to the rarity of the condition, treatment outcomes are only reported anecdotally through case reports/series or collectively with cohorts of other CNV causes. Therefore, an integration of evidence

is needed to understand and optimize treatment in this disease group.

Condition being studied Choroidal neovascularization is the pathological formation of new blood vessels between the inner layer of Bruch's membrane and the outer layer of the sensory retina, causing visual impairment. These vascular lesions can occur secondary to various ocular diseases, including optic disc drusen. Optic disc drusen are calcified deposits in the anterior portion of the optic nerve head that are present in 2% of the population. They are typically asymptomatic but are associated with different vascular complications such as ischemic optic neuropathy and choroidal neovascularization.

METHODS

Search strategy This systemic review is conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020 Statement). Three databases (PubMed, EMBASE, and Web of

Science) are searched for eligible articles. The search strategy includes articles published between 1974 and 2024, based on the earliest report of optic disc drusen-associated choroidal neovascularization on fluorescein angiography imaging to our knowledge. The search terms used include “Optic disc drusen” OR “Optic disk drusen” OR “Optic nerve head drusen” OR “Pseudopapilledema” AND “Neovascularization” in different combinations and strategies depending on the database. In addition, the references sections from the finally selected articles are reviewed to ensure the inclusivity of any missed articles. Only original articles with human participants are included.

Participant or population Patients with choroidal neovascularization secondary to optic disc drusen.

Intervention Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections.

Comparator Observation, laser photocoagulation, photodynamic therapy, and surgery.

Study designs to be included Articles are included if they present original contributions including case reports, case series, case-control observational studies, randomized controlled trials, and letters/correspondences. Review articles, conference abstracts, and animal studies were excluded.

Eligibility criteria Articles are selected if they report each of the following criteria: (1) A diagnosis of optic disc drusen, defined as irregular, lump-bumpy, yellowish deposits in the optic nerve head on fundus exam/photo, or hyper-autofluorescent signal of the optic nerve on fundus autofluorescence imaging, or the presence of a hypo-reflective core with hyper-reflective horizontal lines on optical coherence tomography scans. (2) Presence of signs of choroidal neovascularization (hemorrhagic detachment of the retinal pigment epithelium or active subretinal/sub-RPE leakage on fluorescein angiography). (3) Baseline and follow-up visual acuity. (4) The intervention used to manage the neovascularization, if not observational. Studies that report some eligible subjects as part of a larger study population are included if the data of interest are reported clearly. Studies that report subjective descriptions of the ocular findings, instead of ocular examinations, are excluded to minimize bias.

Information sources PubMed, EMBASE, and Web of Science are the three databases used to search for articles. Additionally, references from the

eligible articles are reviewed to ensure the inclusivity of any missed articles.

Main outcome(s) Visual acuity.

Additional outcome(s) Recurrence of the choroidal neovascularization.

Data management All searched articles are imported into EndNote software, where abstracts are screened for eligibility and duplication. Full texts of the selected articles are reviewed to ensure compliance with the inclusion criteria. The data are then extracted into a Microsoft Excel sheet and analyzed using the R Project for Statistical Computing (R 2023.12.1+402).

Quality assessment / Risk of bias analysis Quality assessment of the included studies is done using the Newcastle–Ottawa Scale for case series and case reports adapted by Murad and coworkers. The tool assesses 4 domains of the report (selection, ascertainment, causality, and reporting) using 5 criteria (excluding items related to adverse drug events). Using a previously described scale (Zhang et al, 2023), we consider the study as “good quality” when all 5 criteria are satisfied, “moderate quality” when 4 are satisfied, and “poor quality” when 3 or fewer are satisfied. Discrepancies are discussed and decided by two authors.

Strategy of data synthesis Data are analyzed using the R Project for Statistical Computing (R 2023.12.1+402; <https://www.r-project.org/>). Descriptive statistics are performed to present patient characteristics. Categorical variables are presented as numbers and percentages. Continuous variables are presented as the median with the range or interquartile range (IQR). The nonparametric Wilcoxon rank-sum test is used to compare continuous variables. A multiple regression model is used to compare variables with possible confounders. A P-value < 0.05 is considered statistically significant.

Subgroup analysis A sub-analysis is performed on the visual outcomes in the pediatric group that received anti-VEGF injections compared to those managed with observation.

Sensitivity analysis Not applicable.

Language restriction No language restriction.

Country(ies) involved The United States.

Keywords Optic disc drusen; peripapillary choroidal neovascularization; neovascular membranes; fluorescein angiography; anti-VEGF; visual acuity.

Contributions of each author

Author 1 - Anas Alkhabaz.

Email: alkhabaz@stanford.edu

Author 2 - Rishita Pujari.

Email: rpujari@stanford.edu

Author 3 - Yulan Ren.

Email: yulanren@stanford.edu

Author 4 - Stephen J. Smith.

Email: smithsj@stanford.edu

Author 5 - Yaping Joyce Liao.

Email: yjliao@stanford.edu